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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,034	09/09/2003	Hiroaki Shizuya	CIT1620-1	3294

28213 7590 04/11/2006

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EXAMINER	
PRIEBE, SCOTT DAVID	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,034	SHIZUYA, HIROAKI	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-14,16-25,27-41 and 43-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-14,16-25,27-41 and 43-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement filed 5/10/04 failed to fully comply with 37 CFR 1.98(a)(2) because a copy of WO 01/11951 referred to therein had not been provided. Applicant's arguments filed 2/8/06 have been fully considered but they are not persuasive. Applicant points out that according to 37 CFR 1.56(b), information that is cumulative of information already of record need not be disclosed. Applicant asserts that EP 1206906 A1 is the European counterpart of and is substantially identical to WO 01/11951, and argues that Applicant need not provide a copy of the PCT document since it is cumulative of the EP document. In response, these arguments are not germane to whether the IDS complied with 37 CFR 1.98(a)(2). They are only germane to whether Applicant has fulfilled their duty to disclose material information as per 37 CFR 1.56, which governs what type of information Applicant has a duty to disclose to the Office. It does not bar Applicant from disclosing more information than is required, nor does it relieve Applicant of their burden to fully comply with 37 CFR 1.98 with respect to information that Applicant does choose to disclose to the Office, which includes the requirement to provide a legible copy of each cited foreign patent document, in this case WO 01/11951.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements

based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Objections

Claims 8, 32 and 41 are objected to because of the following informalities: In each of claims 8, 32, and 41: "oncogene gene"; "suppressor gene gene"; and "P450 gene gene" should be --oncogene--; --suppressor gene--; and --P450 gene--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1, 3-14, 16, 17, 41, and 43-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendment to claim1 and its dependent claims introduces new matter into the application. Claim 1 is directed to a method for making a humanized mouse, and has been amended to replace the term "non-human animal DNA sequence" with "murine DNA sequence" and "non-human animal embryonic stem cell" with "murine embryonic stem cell". Claim 14 has been also amended to replace the term "non-human animal DNA sequence" with "murine DNA sequence." Applicant indicates that this amendment is supported "throughout the specification" and in original claim 15. However, the term "murine" is not used at all in the original specification, and the term "murine" does not mean "mouse," as implied by Applicant. The term

"murine" is a generic term that refers to a large sub-group of rodents found in Eurasia and Africa known as murids, which includes not only *Mus musculus musculus* (European House Mouse), but most rodent species with common names that include the term mouse, rat, jird, and gerbil. There is no evidence from the application as originally filed that Applicant had contemplated or was in possession of DNA or ES cells from this wide array of rodent species, or methods of making a mouse using these materials. Replacing all occurrences of "murine" with "mouse" would be remedial.

Claim 45 is directed to a method of making a "humanized cell" that involves introducing a third DNA construct into a non-human animal cell. Applicant indicates that support for this method is found in original claim 1. However, original claim 1 mentions only a method of making a humanized non-human animal embryogenic stem cell, not a generic "humanized" non-human animal cell, which would include any type of cell such as skeletal myocytes, neurons, fibroblasts, hepatocytes, etc. The original specification also describes only making non-human ES cells and transgenic animals, and fails to mention generic humanized non-human animal cells *per se* or methods of making them. Thus, there is no evidence from the original application that Applicant had contemplated or possessed the method for making a generic "humanized cell" now being claimed.

Claims 1, 3-14, 16, 17, 25, and 27-41 remain rejected and claims 43-46 are rejected under 35 U.S.C. 112, first paragraph, while being enabling for embodiments wherein the non-human animal is a mouse, the non-human animal DNA of the first construct is a mouse genomic DNA comprising mouse DNA, which is orthologous to the human DNA sequence of the second and

third constructs, that is immediately flanked by first and second mouse genomic sequences that are essentially identical to the flanking first and second mouse genomic DNA sequences, respectively, that flank the human DNA sequence in the second construct, the embryogenic stem (ES) cell is a mouse ES cell, the non-human blastocyst is a mouse blastocyst, and the pseudopregnant non-human animal is a pseudopregnant mouse, does not reasonably provide enablement for any other embodiments embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Original claim 42 was inadvertently omitted from the previous rejection. The original grounds of rejection has been modified as required by the amendments to the claims.

Claims 1, 3-14, 16, and 17 are explicitly directed to making a humanized animal, such as is claimed in claims 41, 43, and 44, and the DNA construct produced by the method of claims 25-40 is taught in the specification as being used to make a humanized animal. Claims 45 and 46 are directed to a method of generating a "humanized cell", with claim 46 being limited to a humanized ES cell. The specification (¶ 0048) defines "humanized" animal as being a non-human animal whose genome comprises a human sequence that has replaced analogous, i.e. orthologous, sequences in the genome of the non-human animal. It is presumed that "humanized cell" similarly means that the genome of a non-human animal cell comprises a human DNA sequence in place of an orthologous non-human animal DNA sequence. The only use taught in the specification for a humanized ES cell is to make a humanized animal. As indicated in the preceding rejection, the original specification does not disclose a generic humanized cell, only

humanized ES cells. As explained above, the term murine is not limited to mouse, but rather is vastly broader in scope, encompassing a wide variety of rodent species.

Claims 1, 3-14, 16, 17 are broadly directed to methods for preparing and then introducing a DNA construct (the third) into a murine ES cell, wherein the DNA construct comprises a human DNA sequence flanked by a first and second murine DNA sequences. The claims do not require that the non-human ES cell and the non-human animal DNA be from the same non-human animal, i.e. the ES cell could be a mouse ES cell, and the murine DNA could be from a rat or gerbil. In the case of claims 45 and 46, the non-human cell could be from a mouse, and the non-human DNA could be from a cow, frog or octopus. Presumably, the non-human animal ES cell is from the same species as the "humanized mouse", since it is not possible for a rat or gerbil ES cell, for example, to develop into a different animal such as a mouse. Claim 1 and its dependents broadly embrace an ES cell from any murine animal, and claims 45 and 46 embrace an ES cell from any animal. Claim 1 and its dependents also broadly embrace embodiments wherein the species origin of the ES cell may be different from the mouse blastocyst and pseudopregnant mouse, e.g. a gerbil ES cell. Claim 25 and its dependents are broadly directed to a method for making a DNA construct (the third) for performing homologous recombination in any cell. The construct comprises a human DNA sequence flanked by non-human animal DNA sequences. These same method steps are performed in the method of claim 1, and do not require any particular relationship between the cell, non-human animal DNA sequences and human DNA sequences.

Since the genome of the "humanized" animal or cell must, by definition, contain a human sequence in place of its ortholog in the animal or cell, several constraints are placed on the

relationship between the various non-human animal DNA sequences, the human DNA sequence, and the ES cell (or cell) recited in the claims. As taught in the specification, the construction of the third construct and the subsequent construction of the ES cell and humanized animal is mediated by homologous recombination (not recombination in general, as recited in the claims, which would include illegitimate recombination) first between the first and second non-human animal sequences of the second construct and their homologs in the first construct, and then by homologous recombination between the non-human animal sequences flanking the human sequences in the third construct and their homologs in the genome of the ES cell (e.g. see figs. 3 and 4). Consequently, the only way the non-human ortholog of the human DNA can be replaced by the human DNA present in the third construct is if 1) the non-human animal DNA sequence of the first construct is DNA sequence from the same animal as the non-human animal sequences flanking the human DNA sequence of the second and third constructs; 2) the non-human animal DNA sequence of the first construct comprises homologs of the first and second non-human animal sequences of the second construct that in the non-human animal flank non-human animal DNA orthologous to the human DNA sequence of the second and third constructs (as in instant claim 18), and in the same order and orientation as in the second construct and in the genome of the ES cell; and 3) the non-human animal sequences flanking the human DNA sequence in the first, second and third constructs are from the same species of non-human animal from which the ES cell is obtained.

The method being claimed is basically the same as that used to make targeted gene disruptions in an ES cell for subsequently making a knock-out transgenic animal, where genomic DNA is replaced with foreign DNA such as a marker gene. The difference is that instead of a

marker gene, the genomic DNA is being replaced with its human ortholog, which may contain a marker gene within an intron. At the time of filing, the state of the art held that targeted gene disruption could only be carried out in mouse. Gene targeting requires homologous recombination in cells in culture and the only cells in culture that are totipotent and can contribute to the germline, giving rise to a stable transgenic animal, are totipotent mouse ES cells. The art at the time of filing further held that totipotent ES cells capable of giving rise to a germ-line transgenic animal were not available for any species other than mouse. Campbell et al. (Theriogenology, vol. 47, pp, 63-72, 1997) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cells lines that contribute to the germ line in any species other than mouse (page 65). Wheeler et al. (Theriogenology, Vol. 56, 1345-1369, 2001) taught putative pig ES cells, which produced pig chimeras but there is no disclosure that the chimera gave rise to a pig of the ES cell phenotype (pages 1351-1352), indicating that the ES cells are not totipotent as they are not germline competent. Further, Wheeler states, in reference to ES cells recently isolated and the production of swine and cattle chimera, "validation of totipotency of these embryo-derived ES cell lines awaits conformation" (page 1351, para. 1, last sentence). Prelle et al. (Cells Tissues Organs, Vol. 165, pages 220-236, 1999) states many embryo-derived cell lines resemble morphologically mouse ES cells, and have the ability to differentiate in vitro, but there is no evidence of live born, fertile germ line chimeras in species other than mouse (page 222, col. 2, para. 1, lines 10-16). The specification provides no guidance on the isolation and use of ES cells of species other than mouse in the context of the claimed invention.

Claim 1 and its dependents permit the animal species of origin of the murine ES cell, mouse blastocyst and pseudopregnant mouse to be different. However, such implantation is not predictable, as Fehilly et al. (Nature 307: 634-636, 1984) teach that often two unrelated species cannot carry a live hybrid fetus to term due to factors such as placental abnormalities and maternal immunological reaction against foreign antigens of the conceptus which would be the cause of immediate abortion (see p. 634, 2nd column, 2nd paragraph). Fehilly *et al.* summarize experiments for the production of such animals, and show an extremely low percentage of full term young (see Table 1, p. 635). Although Fehilly *et al.* show that is possible to produce embryos that have been implanted into surrogate mothers of a foreign species, it is clearly an unpredictable process. The specification provides no guidance as to how one would use ES cells, blastocysts and pseudopregnant animals of different species to bring a chimera derived of cells from different animal species to term in a pseudopregnant animals of yet another species. Finally, it is not possible to produce a mouse from a murine ES cell that is not a mouse ES cell.

Therefore, because the specification only teaches gene-targeted replacement and because the prior art teaches that gene targeting can only be performed to make transgenic mice, such a knock-out mice, the specification and art at the time of filing only enable making gene-targeted mice using mouse DNA, mouse ES cells, mouse blastocysts, and pseudopregnant mice. Furthermore, the constraints of the definition of "humanized" in the specification and of homologous recombination dictate a specific relationship between the non-human animal DNA sequences, the human DNA sequences, and genome of the ES cell that is not reflected in the claims as written, i.e. the claims embrace a multitude of embodiments for which no enabling guidance has been provided.

Applicant's arguments filed 2/8/06 have been fully considered but they are not persuasive. Applicant asserts that the amendments to claims 1 and 25 overcome the grounds of enablement. However, as indicated above, replacement of "non-human" with "murine" with respect to the DNA sequences still embraces numerous embodiments that are either inoperative or have not been enabled by the specification. This part of the rejection would be overcome by replacing all occurrences of "murine" with --mouse-- in claim 1, and limiting claim 46 to a --mouse-- ES cell. Also, the amendments do not address the undue breadth of the identity of the murine or non-human animal DNA sequences and the human DNA sequences. This part of the rejection would be overcome by limiting (in claims 1, 25, and 45) the non-human DNA in the first construct and first and second non-human animal DNA of the second and third construct to all be DNA from the same non-human animal, and the cell to be from that same non-human animal. Also, limiting the murine/non-human animal DNA sequence of the first construct to comprise in order and adjacent to one another: the first non-human animal DNA sequence; a non-human animal sequence orthologous to the human DNA sequence; and the second non-human animal DNA sequence, wherein the genome of the non-human animal cell also comprises in order and adjacent to one another: the first non-human animal DNA sequence; a non-human animal sequence orthologous to the human DNA sequence; and the second non-human animal DNA sequence.

Claims 11-14, 16-24, 35-38, 43 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 35 recite the limitation "the intron" in 2. There is insufficient antecedent basis for this limitation in the claim. This part of the rejection also applies to claims 12-14 and 36-38, which depend from claims 11 or 35. Applicant's arguments filed 2/8/06 have been fully considered but they are not persuasive. Contrary to Applicant's assertion, claims 1 and 25 do not recite "intron". It appears that the claims 11 and 35 should depend from claims 10 and 34, respectively.

Claim 16 recites the limitations "the human DNA coding sequence" in lines 1-2 and "the first mouse DNA sequence" in lines 2-3. This part of the rejection also applies to claim 17, which depends from claim 16. Also, claim 17 recites the limitation "the second mouse DNA sequence" in lines 2-3. There is insufficient antecedent basis for these limitations in the claims. Claim 1 recites "a human DNA sequence" and "a first and second murine DNA sequence" not a "human DNA coding sequence" and a "first and second mouse DNA sequence" Amending claim 16 to limit the human DNA sequence to a human coding DNA sequence and amending claim 1 to recite -- mouse-- in place of "murine" in lines 4, 7, and 9 would be remedial.

Claim 18 recites the limitation "the non-human animal" in line 8. There is insufficient antecedent basis for this limitation in the claim. This part of the rejection applies to claims 19-24, which depend from claim 18. Inserting --of a non-human animal-- after "cell" in line 2 of claim 18 would be remedial.

Claim 22 recites the limitation "the flanking sequences" in 1. There is insufficient antecedent basis for this limitation in the claim. Replacing "flanking sequences" with --non-human animal DNA sequences-- would be remedial.

Claim 43 recites the limitation "the gene" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 41 contains a list of genes, and it is unclear which of these is "the gene" referred to in claim 43. Replacement of "is selected" in line 2 of claim 41 with --is a gene selected-- would be remedial.

Claim 44 recites the term "CAR". The specification does not define the term. This term has been used in mammalian gene nomenclature in reference to a variety of different genes, including the coxsackie virus and adenovirus receptor gene, constitutive androstane receptor genes (family), the cell matrix adhesion regulator gene, the CLL-associated RING finger gene, and the cAMP-dependent protein kinase regulatory subunit RIα gene. It is therefore unclear what gene is referred to in claim 44.

Claim Rejections - 35 USC § 102

Claims 18, 21-24, 41 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Divoky et al. (Proc. Natl. Acad. Sci. USA 98(3): 986-991, 30 Jan. 2001).

Divoky discloses a DNA construct for performing homologous recombination in an ES cell, and a transgenic mouse made from the ES cell. The construct comprises the coding region of the human erythropoietin receptor gene (EPOR) from the start codon to the stop codon flanked by first and second mouse genomic DNA sequences. The first mouse DNA sequence is approximately 7 kb of genomic sequence upstream from the start codon of the mouse EPOR gene, and the second mouse DNA sequence is approximately 5 kb downstream from the stop codon of the mouse EPOR gene, i.e. the portion of the mouse EPOR gene from the start to stop codons has been replaced with its human ortholog. The human EPOR coding sequence

comprises a positive selection marker expression cassette (*flox-neo*), inserted within an intron. The DAN construct was used to replace the mouse EPOR coding sequence in one copy of the EPOR gene in a mouse ES cell. These ES cells were then implanted into mouse blastocysts, which was implanted into a pseudopregnant mouse to produce a chimeric "humanized" mice which were then bred to produce transgenic humanized mice carrying one or two copies of the human EPOR coding sequence in place of the orthologous mouse EPOR coding sequence. See page 986, col. 2, through page 987, col. 1; page 987, col. 2; Fig. 1, page 988).

The DNA construct of Divoky was constructed *in vitro* using PCR, restriction enzymes and DNA ligase, rather than by recombination as required in instant claims 1, 3-14, 16, 17, 25, and 27-40. Claims 41 and 43 are directed to a humanized mouse made by the method of claim 1. However, the DNA construct used by Divoky could have been made using the method of claim 1, and the resulting mouse made using such a construct would be the same. To the extent that EPO is a drug used in humans and the EPO receptor is involved in metabolism of EPO, it meets the limitations of claim 43.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

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